REMARKS

Claims 27, 32-40 and 47-52 are active. Independent Claims 27, 32 and 39 have been revised to show that the carrier of the complex is water-soluble and revised to show more clearly that the protein of the complex is not occluded by another substance (the ligand of the complex of Bohannon et al., U.S. Patent No. 5,763,158, is occluded). Support for water-soluble carriers is found in the specification on page 9, lines 3-13 and on page 20, line 10. Support for the requirement that the protein of the complex is free to bind to an analyte is found *inter alia* in Example 9 and in Fig. 1 of the present application, which disclose a complex of carrier-enzyme-protein (goat anti-mouse IgG) which binds to immobilized mouse IgG.

New Claims 47-52 find support in the top paragraph on page 9 of the specification. Therefore, the Applicants do not believe that any new matter has been added. Favorable consideration is respectfully requested.

Objection-Abstract

The Abstract was objected to as containing legal phraseology. This objection is moot in view of the attached Substitute Abstract.

Rejection—Obviousness-type Double Patenting

Claims 27-31 were rejected under the judicially-created doctrine of obviousness-type double patenting as being unpatentable over Claims 1, 16 and 24 of U.S. Patent No. 6,613,564. This rejection is moot in view of the amendment of Claim 27 which now requires a water-soluble carrier.

Rejection—35 U.S.C. §112, second paragraph

Claims 39-46 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite. Independent Claim 39 has been revised to more clearly refer to the incorporating step. While the term "incorporating" is broad, it is not indefinite since one with skill in the art would understand the meaning of this active step in the context of products such as reagents, immunoassay systems, devices or microtiter plates. For example, the complex may be incorporated into a reagent by mixing with a buffer, may be incorporated into a microtiter plate by attachment, or incorporated by inclusion as one ingredient in an assay kit. Accordingly, the Applicants respectfully request that this rejection be withdrawn.

Rejection—35 U.S.C. §102

Claims 27-36 and 39-46 were rejected under 35 U.S.C. §102(b) as being anticipated by Bohannon et al., U.S. Patent No. 5,763,158. This rejection is moot in view of the limitation of the claims to water-soluble carriers, since Bohannon only discloses insoluble carriers (supports), such as glass and plastic beads, see e.g., col. 4, line 67-col. 5, line 3.

The Bohannon et al. complex in Fig. 1 also differs from the complex of the present invention because the ligand is occluded or bound by an antibody. This blocking or occlusion of the ligand is an essential element of the Bohannon complex in Fig. 1. As disclosed in col. 5, lines 9-12, the Bohannon protein "binding site **10** also has a mAb **16** bound to the ligand portion **121** of the complex **12** in such a manner that the mAb 16 at least partially blocks access of a substrate 18 to the enzyme's active site **122**".

When an analyte is added to this water-insoluble complex of Bohannon, the analyte competitively displaces the monoclonal antibody **16**, thus unblocking the enzyme, which may then contact a substrate which produces a colorimetric or luminescent reaction. Thus, the

blocked ligand is a critical component of the Bohannon complex in Fig. 1. On the other hand, the complex of the present invention is required to have a protein which is unblocked and which may bind directly to an analyte. Once the complex of the invention binds to an analyte, such as the immobilized mouse IgG in Example 9, a substrate is added to generate a signal, such as a color reaction.

The attached Sheet graphically compares the complex of the invention (A) with that of Fig. 1 in Bohannon (B). As shown in (B) the Bohannon ligand (shown as a black rectangle) is blocked by an antibody (mAb). In (A) the protein (depicted as an antibody) is free to bind to an analyte. As shown, the complexes of the invention are structurally and functionally distinct from those of Bohannon since they contain an unblocked protein which may bind directly to an analyte.

The following remarks elaborate further on the above differences between the Bohannon complexes and those of the invention.

When a target substance is present in an assay sample, the target substance is bound to mAb (monoclonal antibody): an example of the protein of the complex in the present invention. On the contrary in Bohannon, when a target substance is present in an assay sample the mAb separates from the ligand of the complex of Bohannon et al. and then the thus-separated mAb binds to the target substance, as described in Bohannon, col. 5, lines 6-23:

> A preferred embodiment of the binding site is illustrated in FIG. 1. The binding site 10 comprises two identical ligand-enzyme complexes 12 attached to a solid support 14 via a linker 141. The binding site 10 also has a mAb 16 bound to the ligand portion 121 of the complex 12 to in such a manner that the mAb 16 at least partially blocks access of a substrate 18 to the enzyme's active site 122. The mAb 16 is capable of binding both to the ligand 121 and to the target molecule but has a greater binding affinity for the target molecule than for the ligand 121. Thus, as illustrated 15 in FIG. 2, when the binding site shown in FIG. 1 is exposed to a substrate 18 for the enzyme portion 123 of the complex 12 and to a target molecule

> 20 (FIG. 2) with a specific binding site 201 for the mAb 16, the competing target molecule 20 displaces the mAb 16 from the ligand 121, 20 thereby allowing the exposed enzymatic active site 122 to react with the substrate 18 to generate a color precipitate or light.

The Official Action states:

> With respect to claims 33-35, Bohannon et al. teach that the protein with specific binding potency is a polyclonal antibody or monoclonal antibody (See Figure 1-2; claim 4).

However, the protein with specific binding potency in Figs. 1 and 2 and in claim 4 is mAb (monoclonal antibody) conjugated to a ligand of the complex of Bohannon et al., as seen from the description of lines 6-23 in column 5:

> complex. A preferred, embodiment of the binding site is illustrated in FIG. 1. The binding site 10 comprises two identical ligand-enzyme complexes 12 attached to a solid support 14 via a linker 141. The binding site 10 also has a mAb 16 bound to the ligand portion 121 of the complex 12 in such a manner that the mAb 16 at least partially blocks access of a substrate 18 to the enzyme's active site 122. The mAb 16 is capable of binding both to the ligand 121 and to the target molecule but has a greater binding affinity for the target molecule than for the ligand 121. Thus, as illustrated in FIG. 2, when the binding site shown in FIG. 1 is exposed to a substrate 18 for the enzyme portion 123 of the complex 12 and to a target molecule 20 (FIG. 2) with a specific binding site 201 for the mAb 16, the competing target molecule 20 displaces the mAb 16 from the ligand 121, thereby allowing the exposed enzymatic active site 122 to react with the substrate 18 to generate a color precipitate or light.

and claim 4:

> 4. The method of claim 1, wherein at least one of the known binding sites further comprises a mAb bound to the ligand and at least partially blocking the active site of the enzyme, wherein said mAb has a greater binding affinity for the target antigen or antibody than for the ligand.

Said mAb is not conjugated to an enzyme, but conjugated to a ligand in the complex of Bohannon et al., as explained previously. On the contrary, a protein with specific binding potency is conjugated to an enzyme in the complex of the present invention.

The Official Action indicates:

> With respect to claim 32 and 39, Bohannon et al. teach isolating or recovering the carrier-enzyme-protein complex for determining the activity of the complex for screening antibodies (Col. 10, line 15-25).

Bohannon et al. teach in the description of line 6 from the bottom in column 8 to column 10 as follows:

(1) to express an antigen site (peptide) of the envelope protein of a virus (each of-Ebola, Hanta and Lassa viruses) in the. form of a fusion protein — maltose binding peptide-AP (alkaline phosphatase) — by genetic engineering using a plasmid. Said maltose is separated therefrom to generate a complex composed of peptide and AP as described in lines 15-18 in column 10. The thus-obtained complexes are "The isolated peptide-AP complexes" as described in line 19.

(2) to assay the thus-obtained complexes for enzyme activity and to use for screening monoclonal antibodies as described in lines 19-29. This screening is carried out to find monoclonal antibodies suitable to be conjugated to a ligand (i.e., the peptide of the peptide-AP complex). A suitable mAb (monoclonal antibody) is described in lines 29-33.

(3) to couple the peptide-AP complex to beads (an example of the support (14) of the complex in Fig. 1) and then to bind mAb to the peptide-AP-bead as described in lines 37-48. Thus, the complex of mAb-ligand (peptide)-enzyme (AP)-support (bead) as shown in Fig. 1 is formed.

As understood from the above explanation, it is apparent that the complex in lines 15-25 is not "the carrier-enzyme-protein complex" as indicated by the Examiner, and that the description of line 15-25 does not teach the invention claimed in claim 32.

The Official Action states as follows:

> With respect to claim 36, the target molecules include virus microorganism which inherently contain sugar chain on the surface for the recognition of the protein (See claim 28-29).

Bohannon et al. describe the process for preparing the known binding sites specific for the target molecules recited in claim 29 — i.e., Ebola virus, Hanta virus and Lassar virus — in the description of line 6 from the bottom in column 8 to column 10. In the process, the antigenic sites (peptides) of the envelope proteins of these viruses are prepared by genetic engineering using plasmids utilizing synthetic peptides and obtained in the form of "peptide-AP fusion protein". Further, mAb, which is more-specific for native viral protein antigen than for the peptide of the complex of peptide-AP, is found by screening and then conjugated to said peptide, followed by coupling to beads. Thus, the known binding sites as shown in Fig. 1 are formed. As understood from the above explanation, it is apparent that Bohannon et al. do not teach that a protein with specific binding potency to a sugar chain is conjugated to an enzyme conjugated to a support.

In view of the amendments to the present claims which distinguish the complexes which contain an unblocked protein from the complexes of Bohannon, the Applicants respectfully request that this rejection be withdrawn.

Rejection—35 U.S.C. §103

Claim 36 was rejected under 35 U.S.C. §103(a) as being unpatentable over Bohannon et al., U.S. Patent No. 5,763,158, in view of Chichibu et al., U.S. Patent No. 5,019,498. This rejection is moot in view of the amendments above.

Bohannon does not apply, in view of amendments to the claims as discussed above in response to the anticipation rejection.

Chichibu does not disclose or suggest a carrier-enzyme-protein complex with a water-soluble carrier. Moreover, col. 2, lines 53-55 indicate that the Chichibu assay methods start by binding hyaluronic acid to a solid phase and thus do not suggest water-soluble carrier as

required by the present claims. Accordingly, the Applicants respectfully request that this rejection now be withdrawn.

Rejection—35 U.S.C. §103

Claim 38 was rejected under 35 U.S.C. §103(a) as being unpatentable over Bohannon et al., U.S. Patent No. 5,763,158, in view of McClintock, et al., U.S. Patent No. 5,833,924. This rejection is moot in view of the amendments above.

Bohannon does not apply, in view of amendments to the claims as discussed above in response to the anticipation rejection.

McClintock was cited as disclosing a biotin-binding protein. However, it does not suggest the product of the present invention which contains a water-soluble carrier in combination with an enzyme and protein. Accordingly, the Applicants respectfully request that this rejection now be withdrawn.

CONCLUSION

In view of the above amendments and remarks, the Applicants respectfully submit that this application is now in condition for allowance. Early notification to that effect is earnestly solicited.

Respectfully submitted,

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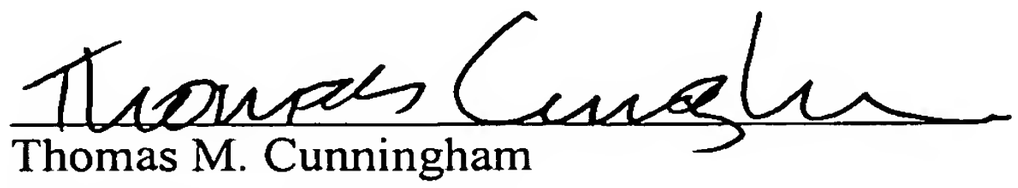

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